
Recommended Warning for Over-the-Counter Acetaminophen-Containing Drug Products and Labeling Statements Regarding Serious Skin Reactions

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact Emily Baker at 301-796-7524.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**November 2014
Compliance**

*Contains Nonbinding Recommendations
Draft—Not for Implementation*

Recommended Warning for Over-the-Counter Acetaminophen-Containing Drug Products and Labeling Statements Regarding Serious Skin Reactions

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

FDA is informing manufacturers, members of the medical and scientific community, and other interested persons that at this time we do not intend to object to the marketing of single- and combination-ingredient, acetaminophen-containing, nonprescription (commonly referred to as over-the-counter (OTC)) drug products bearing a warning as described in this guidance (see section III, Discussion and Policy) alerting consumers that the use of acetaminophen may cause severe skin reactions. This guidance is intended to apply to single- and combination-ingredient acetaminophen-containing products marketed under the Tentative Final Monograph (TFM) for Internal Analgesic, Antipyretic, and Antirheumatic (IAAA) Drug Products for Over-the-Counter Human Use, published in the *Federal Register* (53 FR 46204, November 16, 1988).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Acetaminophen, included in many prescription and OTC products, is a common active ingredient indicated to treat pain and reduce fever. On August 1, 2013, FDA issued a Drug Safety Communication (DSC) informing the public that use of acetaminophen has been associated with

¹ This guidance has been prepared by the Division of Nonprescription Regulation Development in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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40 a risk of rare but serious skin reactions.² These skin reactions, including Stevens-Johnson
41 Syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis, can be
42 fatal.

43
44 The DSC explained that reddening of the skin, rash, blisters, and detachment of the upper surface
45 of the skin can occur with the use of drug products that contain acetaminophen. These skin
46 reactions can occur with the first-time use of acetaminophen or at any time while it is being
47 taken. FDA advised health care professionals to be aware of this rare risk and consider
48 acetaminophen, along with other drugs already known to have such an association, when
49 assessing patients with potentially drug-induced skin reactions. FDA also advised that anyone
50 who develops a skin rash or reaction while using acetaminophen or any other pain reliever/fever
51 reducer should stop taking the drug and seek medical attention right away. Furthermore, the
52 announcement advised that anyone who has experienced a serious skin reaction when taking
53 acetaminophen in the past should not take the drug again and should contact their health care
54 professional to discuss alternative pain relievers/fever reducers.

55
56 In the announcement, FDA stated that it planned to require manufacturers of acetaminophen-
57 containing prescription drug products to include a warning statement on the product labels to
58 address the risk of serious skin reactions and that it would request the same warning be added by
59 manufacturers of OTC acetaminophen-containing drug products marketed under an approved
60 application. In the fall of 2013, FDA sent letters to manufacturers holding new drug applications
61 (NDA) and abbreviated new drug applications (ANDA) requiring in some cases and requesting
62 in others that the language recommended below be included on the labeling for all products (both
63 prescription and OTC) containing acetaminophen marketed under NDAs and ANDAs. At this
64 time, most of the requested labeling changes have been made by the relevant manufacturers.

65
66 FDA also indicated that it planned to encourage manufacturers of acetaminophen-containing
67 drug products marketed under the TFM to similarly add a warning about serious skin reactions to
68 the product labels.

69
70 **III. DISCUSSION AND POLICY**

71
72 FDA recommends that manufacturers of all acetaminophen-containing OTC drug products
73 marketed pursuant to the TFM for IAAA Drug Products (both single- and combination-
74 ingredient acetaminophen products) include language in labeling warning consumers that
75 acetaminophen may cause severe skin reactions.

76
77 At this time, FDA does not intend to object to the marketing of products containing the following
78 warning language described below:

79
80 Allergy alert: acetaminophen may cause severe skin reactions. Symptoms may
81 include: [bullet] skin reddening [bullet] blisters [bullet] rash

² FDA Drug Safety Communication: FDA warns of rare but serious skin reactions with the pain reliever/fever reducer acetaminophen. <http://www.fda.gov/Drugs/DrugSafety/ucm363041.htm>.

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82 If a skin reaction occurs, stop use and seek medical help right away.

83
84 This guidance does not address alternative warning language that may otherwise misbrand the
85 product.

86
87 This recommended warning should appear under the “Warnings” heading section of the Drug
88 Facts label under the subheading “Allergy Alert” and directly follow the liver warning (21 CFR
89 201.326) on acetaminophen-containing drug products. FDA recommends that this warning be
90 included on all packaging configurations.

91
92 **IV. EXAMPLE OTC DRUG FACTS LABEL WITH RECOMMENDED WARNING**

Drug Facts	
Active Ingredient (in each [insert dosage form])	Purpose
Acetaminophen XXX mg.....	Pain reliever/fever reducer
Uses (Insert as described in an applicable OTC drug monograph or approved drug application.)	
Warnings	
Liver warning: This product contains acetaminophen. Severe liver damage may occur if you take: <ul style="list-style-type: none">more than [insert quantity and dosage form] in 24 hours, which is the maximum daily amountwith other drugs containing acetaminophen3 or more alcoholic drinks every day while using this product	
Allergy alert: acetaminophen may cause severe skin reactions. Symptoms may include: <ul style="list-style-type: none">skin reddeningblistersrash	
If a skin reaction occurs, stop use and seek medical help right away.	
Do not use <ul style="list-style-type: none">with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.for more than 10 days for pain unless directed by a doctorfor more than 3 days for fever unless directed by a doctor	
Ask a doctor before use if you have <ul style="list-style-type: none">liver disease	
Ask a doctor or pharmacist before use if <ul style="list-style-type: none">you are taking the blood thinning drug warfarin	
Stop using and ask a doctor if <ul style="list-style-type: none">symptoms do not improvenew symptoms occurpain or fever persists or gets worse	
If pregnant or breast-feeding, ask a health professional before use.	
Keep out of reach of children. In case of accidental overdose, get medical help or contact a Poison Control Center right away. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.	
Directions (Insert as described in an applicable OTC drug monograph or approved drug application.)	
Other Information (Insert any additional information that is not included under the other subheadings but which is required or is made optional under an OTC drug monograph(s), other OTC drug regulation(s), approved drug	

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<i>application, statute, or OTC drug guidance.)</i>
Inactive Ingredients <i>(Insert a list of each inactive ingredient, using its established name.)</i>
Questions or Comments <i>(Insert optional heading used to provide a telephone number of a source to answer questions about the drug product or to receive reports of adverse events associated with the use of the drug product.)</i>

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